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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/591,279	Applicant(s) DEHESH ET AL.	
	Examiner David J. Steadman	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) 1-3 and 13-16 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 4-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 and 7 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Application Status

Claims 1-16 are pending in the application.

Election/Restrictions

1. Applicants election with traverse of Group II, claims 4-12, drawn to an amino acid sequence of a β-ketoacyl-ACP-synthase (KAS) in Paper No. 6, filed 10/29/01 is acknowledged.

Applicants traverse the restriction requirement by arguing that all pending claims should be co-examined as the examiner has not shown that a serious burden of search would result from examination of all pending claims. Applicants further argue that at least Groups II and III should be co-examined because they are related as nucleic acid and encoded polypeptide and would not result in a serious burden of search on the examiner. Applicants' argument is not found persuasive. As stated in a previous Office action (Paper No. 5), "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP 808.02" (see MPEP 803). Each of the inventions listed previously in Paper No. 5 as Groups I-IV have *separate classification*. Group I is classified in 435/440; Group II is classified in 435/193; Group III is classified in 435/320.1; and Group IV is classified in 435/455. Furthermore, although a polynucleotide and the encoded polypeptide are related, they are *distinct inventions* because the polypeptide product can be made by other and materially distinct processes, such as *in vitro* synthesis. Also, a polynucleotide can be used for processes other than polypeptide expression such as a probe in hybridization assays. Therefore, because each of the inventions listed as Groups I-IV is patentably distinct, has a separate classification, and requires a separate search, co-examination of all inventions would result in a serious burden of search on the examiner.

Claims 1-3 and 13-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Sequence Compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). Applicant is requested to return a copy of the attached Notice to Comply with the response.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: non-initialed and/or non-dated alterations have been made to the declaration. See 37 CFR 1.52(c).

Drawings

4. The drawings submitted with this application have not been reviewed by a draftsperson at this time. Upon allowance of the claims, the draftsperson will perform a review. Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

Specification/Informalities

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Mutant E. coli KAS II With Altered Substrate Specificity".See MPEP § 606.01.

6. The drawings are objected to by the examiner because Figure 12-2 is not present with the instant application.

Claim Objections

7. Claims 4, 6, 8, and 9 are objected to because of the recitation of "β-ketoacyl-ACP synthase" in claims 4 and 8 and "E. coli" in claims 6 and 9. Abbreviations should not be recited in the claims without at least once reciting the entire phrase, i.e., "β-ketoacyl-[acyl carrier protein] synthase" and "Escherichia coli", respectively, for which the abbreviations are used. Appropriate correction is required.

8. Claim 8 and 12 are objected to because of the following informalities: the term "residue" is grammatically incorrect and should be replaced with, for example, "residues". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 4-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 4 (claims 5-7 dependent therefrom) is confusing in the recitation of the term "amino acid sequence encoding a β-ketoacyl-ACP synthase protein". Nucleic acids and not amino acids encode polypeptides. It is suggested that applicants clarify the meaning of the claim by, for example, by replacing the term "encoding" with "of".

11. Claims 5-7, 9, and 11 are confusing in the recitation of "sequence is obtained from" referring to an altered KAS polypeptide. The application discloses that the altered KAS polypeptides were generated by mutating the polynucleotide encoding wild-type E. coli KAS II. Therefore, such mutant sequences would not be directly "obtained from" prokaryotic, E. coli, or plant sources. It is suggested that applicants clarify the meaning of the claims.

12. Claims 4-12 are unclear in the recitation of "has at least one substitution, insertion or deletion of at least one amino acid residue" because applicants have not provided the amino acid sequence of a reference KAS polypeptide necessary for a determination of the position of the claimed mutations, substitutions, and/or deletions and therefore, to define the metes and bounds of the claims. The incorporation of this essential material by merely providing descriptions of the terms "β-ketoacyl-ACP synthase" and "KAS" in the specification and references disclosing the sequences of KAS polypeptides are improper. Because KAS has been isolated from various species and variants of KAS exist in the art, applicants should provide sequences of the KAS polypeptides to which these terms refer. See MPEP § 2420 for the requirements for patent applications containing amino acid sequences.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 4-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 4-12 are rejected because the claims recite KAS polypeptides with insertions, deletions, and/or substitutions with (claims 4-7) or without (claims 8-12) altered substrate specificity that have not been disclosed in the specification. The specification teaches the structure of only a single representative

species of KAS polypeptides with altered substrate specificity, namely, E. coli KAS II with the mutations set forth at Figure 7 of the instant specification. The specification fails to disclose any other KAS polypeptides with insertions, deletions, and/or substitutions with or without altered substrate specificity by any identifying structural characteristics or properties other than the functionality of being mutant KAS polypeptides with or without altered substrate specificity. Given the lack of description of additional representative species of KAS polypeptides with or without altered substrate specificity as encompassed by the genus of the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

14. Claims 4-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for E. coli KAS II with amino acid substitutions at positions 108, 111, 114, 133, 193, and 197 as set forth in Figure 7, thereby resulting in altered substrate specificity for acyl-ACP, does not reasonably provide enablement for a KAS obtained from *any* organism with *any* substitution, insertion, or deletion with altered substrate specificity (claim 4), and optionally wherein the KAS is *any* prokaryotic KAS (claim 5), *any* E. coli KAS (claim 6), or *any* plant KAS (claim 7) or a KAS obtained from *any* organism with *any* substitution, insertion, or deletion of *any* of residues 105-120, 130-140, 190-205, and 340-400 (claim 8), and optionally wherein the KAS is *any* E. coli KAS (claim 9) and optionally wherein the substitution, insertion, or deletion of *any* E. coli KAS is at residues 108, 111, 113, 114, 133, 138, 193, 197, and 203 (claim 10), and optionally wherein the KAS is *any* plant KAS (claim 11) and optionally wherein the substitution, insertion, or deletion of *any* plant KAS is at residues 110, 113, 115, 116, 134, 139, 198, and 204 (claim 12). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claim 4 is so broad as to encompass a KAS obtained from *any* organism with *any* substitution, insertion, or deletion with altered substrate specificity. The remaining claims further restrict one or more of the sources of the KAS (e.g., procaryote, E. coli, or plant) or the position of at least one mutation but none of the claims limit the numbers of mutations present in the claimed polypeptide such that the scope of the claims appears to include *any* polypeptides with the recited functional limitations, i.e., KAS activity with or without altered substrate specificity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of KAS polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to E. coli KAS II with substitutions at positions 108, 111, 114, 133, 193, and 197 as set forth in Figure 7, thereby resulting in an altered acyl-ACP substrate specificity.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a KAS obtained from *any* organism with *any* substitution, insertion, or deletion with altered substrate specificity because the specification does not establish: (A) regions of the KAS polypeptide structure of any organism which may be modified without affecting activity; (B) the general tolerance of *any* KAS from *any* organism, *any* KAS from *any* prokaryotic or plant source or *any* KAS from E. coli to modification and extent of such tolerance as mutations of a polypeptide's amino acid sequence from one source, e.g., E. coli, will not necessarily have the same biological effect(s) in the corresponding enzyme from another source, e.g., plant, particularly in the case of E. coli KAS II and Cuphea pulcherrima KAS IV where the corresponding amino acids in the hydrophobic pocket are not identical (see for example page 29 and Figure 11 of the instant specification) and thus one of skill in the art would not have a reasonable expectation of success that similar mutations in C. pulcherrima KAS IV would produce the desired biological activity; (C) the general tolerance of *any* E. coli KAS to modification and extent of such tolerance as mutations in E. coli KAS II will not necessarily have the same biological effect(s) in other E. coli KAS polypeptides, e.g., Moche et al. (J Biol Chem 274:6031-6034) dislcose that amino acid sequences for E. coli KASIII show very low degrees of sequence identities to E. coli KASI and KASII (page 6033, left bottom); (D) a rational and predictable scheme for modifying specificity of the co-substrate malonyl-ACP; (E) a rational and predictable scheme for mutating residues of *any* KAS from *any* organism, *any* prokaryotic or plant source, or E. coli other than residues 108, 111, 114, 133, 193, and 197 of wild-type E. coli KAS II with the mutations set forth in Figure 7 with an expectation of obtaining the desired acyl-ACP substrate specificity; (F) the predictability that mutating residues 113, 138, and/or 203 of *any* E. coli KAS or E. coli KAS II or residues 115, 139, and/or 204 of *any* plant KAS will generate a KAS with the desired biological effect as applicants have not disclosed such mutations and their resulting effects on any of *any* E. coli KAS, E. coli KAS II, or *any* plant KAS; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims

broadly including a KAS obtained from *any* organism with *any* substitution, insertion, or deletion with altered substrate specificity, and optionally wherein the KAS is *any* prokaryotic KAS, *any* E. coli KAS, or *any* plant KAS or a KAS obtained from *any* organism with *any* substitution, insertion, or deletion of *any* of residues 105-120, 130-140, 190-205, and 340-400, and optionally wherein the KAS is *any* E. coli KAS and optionally wherein the substitution, insertion, or deletion of *any* E. coli KAS is at residues 108, 111, 113, 114, 133, 138, 193, 197, and 203, and optionally wherein the KAS is *any* plant KAS and optionally wherein the substitution, insertion, or deletion of *any* plant KAS is at residues 110, 113, 115, 116, 134, 139, 198, and 204. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (IDS reference; EMBO J 17:1183-91) in view of Edwards et al. (IDS reference AO; FEBS Letters 402:62-6). Claims 8 and 9 are drawn to a KAS amino acid sequence with at least one substitution, insertion, or deletion of at least one amino acid selected from residues 105-120, 130-140, 190-205, and 340-400 (claim 8), and optionally wherein the sequence is an E. coli KAS (claim 9).

Edwards et al. teach cloning of the fabF gene encoding E. coli KAS II and suggest that cloning of the gene encoding E. coli KAS II "provides a ready means to assess the effect of specific mutations in the KAS genes on their enzymatic activities" (page 66, bottom right).

Huang et al. teach the crystal structure of native E. coli KAS II and teach amino acid residues at the active site and potentially involved in binding and/or catalysis include, among other residues, positions 202, 205, 340, 349, 375, and 398-400 (pages 1186-89).

Therefore, it would have been obvious to one of ordinary skill in the art to replace any of residues 202, 205, 340, 349, 375, and 398-400 with other residues altering side chain characteristics such as hydrophobicity or volume because of the teachings of Edwards et al. and Huang et al. One would have been motivated to replace any of residues in order to isolate residues and their roles in catalysis by analyzing the effects of specific mutations in the E. coli KAS II polypeptide on its enzymatic activity as suggested by Edwards et al. One would have a reasonable expectation of success for substituting any of residues 202, 205, 340, 349, 375, and 398-400 because of the results of Edwards et al. and Huang et al. Therefore, claims 8 and 9, drawn to a KAS amino acid sequence with at least one substitution, insertion, or deletion of at least one amino acid selected from residues 105-120, 130-140, 190-205, and 340-400, and optionally wherein the sequence is an E. coli KAS would have been obvious to one of ordinary skill in the art.

16. Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moche et al. (IDS reference AL; J Biol Chem 274:6031-34) in view of Edwards et al. (IDS reference AO; FEBS Letters 402:62-6). Claims 8-10 are drawn to a KAS amino acid sequence with at least one substitution, insertion, or deletion of at least one amino acid selected from residues 105-120, 130-140, 190-205, and 340-400 (claim 8), and optionally wherein the sequence is an E. coli KAS (claim 9), and optionally wherein the substitution, insertion, or deletion is at residues 108, 111, 113, 114, 133, 138, 193, 197, and 203 (claim 10).

Edwards et al. teach cloning of the fabF gene encoding E. coli KAS II and suggest that cloning of the gene encoding E. coli KAS II "provides a ready means to assess the effect of specific mutations in the KAS genes on their enzymatic activities" (page 66, bottom right).

Moche et al. teach the crystal structure of E. coli KAS II complexed with the antibiotic cerulenin (pages 6033 and 6034), that the E. coli KAS II-cerulenin complex can be considered to mimic the intermediate formed upon reaction of KAS with the acyl-ACP substrate (page 6032), and that the amino acid residues involved in cerulenin binding are the hydrophobic residues G107, I108, L111, F 133, V134, I138, A162, A193, G198, F202, L342, and F400 (page 6032, middle right). Moche et al. teach that a G to S mutation in Saccharomyces cerevisiae fatty acid synthase (FAS), corresponding to G107 in E. coli KAS II, results in cerulenin resistance (page 6033, right). Moche et al. teach that "[t]here are few exceptions to the inhibition of KAS by cerulenin" and teach that only FAS of Cephalosporium caerulens and KAS III are cerulenin resistant (page 6033, left). Moche et al. teach exchange of G for S at the corresponding position 107 introduces steric hindrance and influences polarity in the hydrophobic binding site.

Therefore, it would have been obvious to one of ordinary skill in the art to replace any of residues G107, I108, L111, F 133, V134, I138, A162, A193, G198, F202, L342, and F400 with an amino acid exhibiting a hydrophilic side chain and particularly to replace G at position 107 of E. coli KAS II with S because of the teachings of Edwards et al. and Moche et al. One would have been motivated to replace any of the hydrophobic residues G107, I108, L111, F 133, V134, I138, A162, A193, G198, F202, L342, and F400 with an amino acid with a hydrophilic side chain in order to analyze the effects of altering the hydrophobicity of the E. coli KAS II hydrophobic binding site. In particular, one would have been motivated to replace G at position 107 of E. coli KAS II with S in order to analyze the importance of G107 in cerulenin binding and/or to generate a cerulenin-resistant E. coli KAS II. One would have a reasonable expectation of success for substituting any of residues G107, I108, L111, F 133, V134, I138, A162, A193, G198, F202, L342, and F400 because of the results of Edwards et al. and Moche et al. Therefore, claims 8-10, drawn to a KAS amino acid sequence with at least one substitution, insertion, or deletion of at least one amino acid selected from residues 105-120, 130-140, 190-205, and 340-400, and optionally wherein

the sequence is an E. coli KAS, and optionally wherein the substitution, insertion, or deletion is at residues 108, 111, 113, 114, 133, 138, 193, 197, and 203 would have been obvious to one of ordinary skill in the art.

Conclusion

17. No claim is in condition for allowance. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 6:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

Rebecca Prouty

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600